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Open Peer Review of: Association Between Aluminum Exposure from Vaccines Before Age 24 Months and Persistent Asthma at Age 24 to 59 Months

Martin Kulldorff

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Abstract

In an observational study by Daley et al. (2023), vaccine-related aluminum exposure in children was associated with more asthma. This is an important and well conducted study using excellent data and solid methods. The effect seen may be due to aluminum per-se, but it could also be an artifact if asthma is just caused by the DTaP vaccines, which has the highest aluminum, or it could be caused by non-live vaccines whether they contain aluminum or not. As another possibility, the effect could be due to some confounding variable not accounted for in this observational study. Further exploration is warranted.

Introduction

Vaccines are an important public health intervention, but after the Covid vaccine mandates, general vaccine confidence has plummeted. Some vaccines contain an aluminum adjuvant to enhance immune response. Aluminum containing vaccines have become a topic of contention, reaching the pages of New York Times and other media.[1]

In 2023, the Daley et al.[2] published an observational study where vaccine-related aluminum exposure in young children was associated with an increased risk of persistent asthma. In children with eczema, each additional mg of aluminum increased asthma risk by 26% (95% CI: 7%-49%), while it increased by 19% (95% CI:14%-25%) in children without eczema.

Despite coming from the Vaccine Safety Datalink (VSD),[3] the crown jewel of vaccine safety research, the study was criticized by renowned vaccine scientist Dr. Paul Offit, who stated that the paper was 'critically flawed' and 'that should never be published, because it offers nothing to our understanding of vaccines.'[4] Since it was published in Academic Pediatrics, a peer-reviewed journal, some reviewers presumably liked it, but those reviews are not open to the public. Considering that this is an important topic of public interest, here is an open peer review of the article that anyone can read.

Study Strengths

Without any proper randomized trials on the topic, aluminum in vaccines must be studied using observational data. As opposed to the safety study of a single vaccine, aluminum is a component of the vaccine schedule, which is more complex to study methodologically.[5] This observational study has many strengths, and as such, it could serve as a template for how to conduct vaccine safety study on certain aspects of the vaccine schedule.

Total aluminum exposure was appropriately treated as a continuous variable, calculated by summation of the aluminum content in the different vaccines given to the children. This maximizes statistical power for the aluminum hypothesis.

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The data is of very high quality. Using electronic health records, most vaccinations and most cases of asthma were captured and independently of each other. An important strength is that the researchers defined 24 months of age as a dividing time, only considering exposures before that time and only considering outcomes afterwards.

The study is well powered, and the statistical analyses were thoroughly conducted and proper. The analyses were adjusted for several potential confounders: age, sex, premature birth, ethnicity, medical complexity, health care utilization and geographical study site.

Rather than stratifying by eczema status, one wish that the authors had combined all children in one single analysis, adjusting for eczema status. That would have generated a more precise confidence interval.

Interpretation

If the result had been negative, not showing any association, that would have provided evidence against the hypothesis that aluminum in vaccines increases, but that was not the result.

While an increase of around 19% and 26% respectively may seem small, note that this is the increased risk for each additional milligram (mg) of aluminum. The children's average aluminum exposure was around 4 mg, and if one instead estimates the increased risk for each additional 4 mg, the point estimates show more than a two-fold excess risk. That is the estimate more relevant to public health.

Considering two independent analyses that both show a clear association, for children with and without eczema, random chance is un unlikely explanation for the results. There are three other potential explanations. The first is that aluminum in vaccines increases the risk of asthma.

The second is that there is something else vaccine related that causes asthma, which is unrelated to but correlated with aluminum. For example, most aluminum exposure comes from DTaP vaccines. If the DTaP vaccines increase the risk of asthma, then an aluminum analysis may also show an increased risk even if it is just an innocent bystander. Another possibility is that non-live vaccines increase the risk of asthma, whether they contain aluminum or not. From the important work of Stabell Benn and colleagues,[6] we know that vaccines can have non-specific effects unrelated to the targeted disease. While live vaccines have shown positive non-specific effects, non-live vaccines have been associated with increases in all-cause mortality and morbidity.

The third potential explanation is confounding with variables other than those included in the regression model. This could happen if those with an increased risk of asthma are more likely to receive the aluminum containing vaccines. Offit proposed three potential confounders:[4] breast feeding, family history of asthma and air pollution exposure that differ geographically. All three are valid concerns.

Daley et al. did address breast feeding, for which data was available for a small subset of the children. Adjusting for this variable increased the strength of the association between aluminum and asthma, with a larger point estimate. This is because vaccinated children were more likely to have been breast fed, and breast feeding is protective against subsequent development of asthma. Even though the confidence intervals are wider due to smaller sample size, breast feeding is hence unlikely to explain the aluminum-asthma finding.

The other two potential confounders are harder to dismiss without further analyses.

Need for Further Analyses

Vaccine safety research can be likened with the mosaic of a jigsaw puzzle. However good, one observational study is seldom sufficient to make definite conclusions about causality, but multiple studies with different strengths can together reveal an accurate picture just like different pieces of a jig-saw puzzle together can reveal an otherwise hidden picture. So, what are the additional pieces needed?

Since DTaP vaccines contain the most aluminum, it is important to dissect the asthma risk between aluminum and DTaP vaccines. The first step would be to do the same analysis with aluminum replaced by DTaP. Which of the two gives the strongest effect size on asthma? Second, by putting both variables in the same model, we get an estimate of the aluminum effect adjusted for DTaP and an estimate of the DTaP effect adjusted for aluminum. This can then be compared with the original estimates without the other variable in the model, to determine if the point estimates hold up or is weakened by including the other variable in the same regression model. Because of strong correlation between the two variables, the confidence intervals will be wider but that can be partly offset through a combined analysis of

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children both with and without eczema.

Another exposure to consider in a similar manner is the total number of non-live vaccines.

For the association to be explained by air pollution as a confounder, vaccination rates must be higher in high pollution areas. This is easily explored by plotting zip-code or census tract air pollution data against vaccination rates. Even without air pollution data, it is possible to adjust for it by including zip-code or census tract as a categorial variable in the aluminum-asthma regression model. Such geographical data is readily available.

Adjusting for family history is harder. It would be prohibitively expensive to survey all children to determine family history, but a subset may be feasible. Another option may be to link children with the electronic health records of their siblings.

Since different brands of vaccines for the same diseases contain different amounts of aluminum, as the authors show in their Supplemental Table 1, one could conduct a clinical trial where children are randomized to either a high or low aluminum content vaccine schedule, to determine if the higher exposure group has a higher risk of asthma.

Summary

Daley et al. have conducted what is probably the best and most important epidemiological study regarding the safety of aluminum in vaccines. It does not provide definite answers, but it leads the way towards additional studies needed to solve the puzzle. One can only agree with the authors' conclusion that 'additional investigation of this hypothesis appears warranted'.

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